REVIEW
OF
LITERATURE
Review of literature

Despite the fact that smoking is injurious to health, people don't quit smoking for several reasons. Cigarette smoking is a major risk factor for developing diseases such as coronary heart disease, lung cancer, COPD, diabetes and several cardiovascular, pulmonary and ocular diseases.

Prevalence and global patterns of smoking

The rate of smoking is alarmingly increasing world wide. According to world estimates of the year 2003, more than 1.3 billion smokers are present world wide in 2003 in high low and middle income countries. In that 82% of total smokers were from low and middle income countries. Earlier estimates of 1995 indicated a similar pattern, i.e, a vast majority of the world's 1.1 billion smokers were from low and middle income countries. Besides 4.9 million premature deaths occurred due to smoking related illnesses in 2000. For the entire 20th century a cumulative number of tobacco deaths were estimated to be about 100 million. It is also clear from the estimates that here after, there will be 10 million tobacco deaths per year. Furthermore, over the 21st century as a whole 1 billion tobacco deaths are projected which could be avoided if people quit smoking. However reports reveal that quitting remains rare in low income and middle income countries.

In most countries cigarette constitutes the major form of smoked tobacco. On an average world's smokers consume 14 cigarettes each per day and in high income countries. Males and females smoke on an average 20 cigarettes a day. Chinese records reveal that they cultivated and smoked it before the 1st millennium. Later it was spreaded to native populations of Americans in the middle ages. Even when Columbus first
entered America he was offered dried tobacco leaves. Later in the middle of 16th century tobacco was introduced in Europe and subsequently brought to Africa and Asia. Now manufactured cigarettes are gradually replacing other forms of tobacco and tobacco products worldwide. Various forms of tobacco pose greatest health risk since its combustion products are passed and absorbed through oral, pulmonary and vascular systems during puffs.

Human beings are oronasal inhalers. Some smokers strongly and continuously inhale the smoke, while others take smoke with pause. Cigarette smoking is often combined with the simultaneous use of other psychoactive drugs such as alcohol and other substances. Then interactions of smoke with other related constituents are common. However cigarettes are puffed repeatedly in order to keep them on and to make the smoker elite, and in doing so, they probably deliver relatively higher doses of constituents of smoke and tar.

**Forms of tobacco**

<table>
<thead>
<tr>
<th>Types of tobacco</th>
<th>Constituents</th>
<th>Geographical Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bidi</td>
<td>Hand rolled sun cured tobacco</td>
<td>South east Asia, India</td>
</tr>
<tr>
<td>Clove cigarettes</td>
<td>Clove buds and tobacco</td>
<td>China</td>
</tr>
<tr>
<td>Pipes</td>
<td>Sulpa, chilum &amp; Hookli</td>
<td>Clay pipe</td>
</tr>
<tr>
<td>Water pipes</td>
<td>Tobacco covered with Pieces of glowing charcoal</td>
<td>Asia, Egypt, and other middle eastern countries</td>
</tr>
<tr>
<td>Smoke less tobacco</td>
<td>South Asia, USA</td>
<td></td>
</tr>
<tr>
<td>Tobacco chewing</td>
<td>South east Asia, North Africa, Eastern Mediterranean countries.</td>
<td></td>
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</tbody>
</table>
Prevalence of smoking is highest for people aged 30-49 years (37%) and lowest among youth 15-19 and is also relatively low among people aged 60 or older (24%). There is wide variation in smoking prevalence of males and females. The rate is high in males in most countries about 60%. Among females the prevalence of smoking was highest in Europe and central Asia, 1,6,10.

Nowadays most smokers start before age 25, often in childhood and adolescent and most adult smokers start their smoking when they are adolescent and parental separation increases the likely hood that adolescents will start smoking11. Smoking habit has been found to be linked with several demographic variables (such as age, sex, socioeconomic level etc.,) with a number of general behavioral patterns (such as degree and kind of participation in a variety of social activities) with psychological characteristics (such as intelligence, school achievement etc) and with certain personality variables (such as intro and extroversion gregariousness, feeling of inferiority need for status etc12.

Various reports suggest that smoking leads to increased medical costs and lost productivity over the life span11. Besides reduced life span and health expectancy or the other feelings from reports13. Parental smoking is the strongest predictor of smoking among high school/college students and other smoker in general14. Other surveys on tobacco smoking, attributable to mortality reveal that tobacco smoking is the most preventable health risk15. Smoking cessation strategies are also beneficial to reduce mortality and morbidity in normal people and HIV infected persons16,17.

In spite of wide and repeated aggressive campaigns against smoking by many recognized organizations, and efforts and measures to curb smoking and the use of other
tobacco products by raising awareness about negative consequences of chronic smoking on almost all organs and systems of human body, the number of smokers is on increase with the entry of new smokers every year including teenaged boys and girls.

It seems that the developed world largely recognized the devastating effects of chronic smoking, as it affects pulmonary, cardiac, ocular, and vascular functions leading to various forms of cancer. However, smoking is on the rise in developing nations and smoking rates in the developed world remain very high among individuals with alcohol use disorder and other neuropsychiatric disorders.

**Possible benefits of cigarette smoking and aspects of its addiction and tolerance**

Evaluation of the effects of smoking on health would not be proper if beneficiary effects of smoking are not taken into consideration. Due to certain specific constituents such as nicotine cigarette smoke exerts psychoactive, euphoric, reinforcing and produces tolerance to cope with stress. Other useful effects include weight control, mood control and relief of tobacco withdrawal symptoms. Besides the role of smoking in maintenance of good intestinal tone and bowel habits are well documented. Moreover antiobesity effects upon reduced hunger and a possible elevation in blood sugar are reported.

Unlike alcohol and other drugs cigarette smoking or its constituent nicotine does not impair performance in judgement, cognition or motor behaviour. In addition it may slightly improve performance and health of people to cope with daily stress. It is generally asserted that smokers can take self decisions effectively, quickly compared to nonsmokers and the decision taken is also often said to be rapid, apt, bold and also effective to get good results. Recently some more beneficiary effects of smoking/nicotine are coming into light. Cigarette smoke consists of nicotine, nitric
oxide, some aldehydes and other components along with oxidant free radicals. While some of the former constituents exert antioxidant properties and also appear to be neuro protective, others cause damage. Many evidences suggest that cigarette smoking has neuroprotective effects by exerting certain desirable effects in Parkinson's disease and Alzheimer's disease by activating AchR and also by inhibiting MAO activity. Besides cigarette that smokers are less susceptible for Alzheimer's disease and Parkinson's disease.

Smoking is possibly an addiction and/or habituation. Why people do not quit smoking?

Personality and behavioral studies have suggested why some people are more likely to smoke, and what smokers perceive that they derive from smoking tobacco. Addiction to nicotine has been established as the psychopharmacologic mechanism that maintains cigarette smoking behaviour. Smokers often increase smoking intensity, smoking rate or inhalation to maintain levels of nicotine as measured by plasma levels of nicotine in both ad libitum and laboratory smoking settings.

Nicotine is the primary constituent of tobacco that reinforces cigarette smoking behaviour, the leading preventable cause of morbidity and mortality. The acute effects of nicotine responsible for initiation of smoking and onset of dependence are not specifically known; but nicotine's acute effects that influence on subjective mood are associated with increased neuronal activity in nucleus accumbency, amygdale and other brain regions which are believed to be involved in drug reinforcement and dependence in humans. Reports reveal that nicotine stimulates AchRs and inhibits MAO activity which is desirable neuro protective and beneficiary features. The functional tolerance to...
substances of abuse often is temporarily related to escalating drug use and difficulty in stopping drug use is hallmark of dependence. Current criteria of drug dependence highlight the presence of tolerance. Drug tolerance also illustrates adaptive biological processes resulting from repeated drug intake which may be relevant to understanding broader aspects of body functioning. Long term exposure to tobacco smoking leads to attenuation of subjective effects of nicotine, reflecting chronic tolerance that is functional in nature. Chronic tolerance develops to the discriminative stimulus effects of nicotine which may relate to its subjective effects. Processes of adaptation to chronic nicotine intake that lead to dependence are not clear, but chronic tolerance has long been assumed to play a key role.

**Chemistry of cigarette smoke**

The chemical composition of cigarette smoke is complex, with about 4000 known active chemicals and more than 1,00,000 unknown constituents. Of these more than 40 chemical are shown to be carcinogenic, and many others are deleterious to cardiovascular and pulmonary systems and other organs. Among these nicotine, tars, nitrosamines, polycyclic aromatic hydrocarbons, hydrogen cyanide formaldehyde and carbon monoxide are well known constituents of cigarette smoking. Besides many free radical species, aldehydes, peroxides, epoxides, nitrogen oxides, peroxyradicals and other prooxidants exist in gas phase. Although nicotine is the addictive component of cigarette smoke, it should be recognized that effects of cigarette smoking are not equivalent to that of nicotine, as nicotine is one of the several thousand components of cigarette smoke. During the blending and processing of tobacco humectants such as glycerin and propylene glycol are added to increase the moisture holding capacity of tobacco to aid in
processing while flavor in processing while flavor ingredients (nonvolatile aromatic materials like menthol and also foods such as chocolate, cocoa and spices such as vanilla nut mug ginger) are used to enhance flavor of tobacco smoke. Studies conducted by Carmines et al., revealed the presence of various smoke constituents in different concentrations in normal cigarettes and cigarettes containing licorice extracts in TPM (total particulate matter).

From earlier reports it is clear that cigarette smoke contain numerous components. Cigarette smoke constituents can be categorized into two (i) The tar component of cigarette smoke (ii) Gas components of cigarette smoke. Tar components of cigarette smoke contain an estimated $10^{18}$ spins/gram tar. The gas phase consists of as many as $10^{15}$ organic radical per puff.

Cigarette smoke contains polycyclic aromatic hydrocarbon benzo-pyrene and tobacco specific nitrosamine NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) which were demonstrated to be potent carcinogens causing lung cancer in mice, rats, hamsters and also humans. Besides nicotine and carbon monoxide are present in particulate phase and gas phase containing two tobacco nitrosamines NNK and NNN(N'-nitrosonomicotine), bipyridyl amino biphenyl benzoquinone and several other constituents such as naphthalene, phenanthrene, anthracene and pyrene chrysene and some other polycyclic hydrocarbons which even enter the human systems through filtered smoke. It is possible that inhalation of benzo (α) pyrene, NNN or NNK delivers higher concentrations or larger amounts of carcinogens directly to putative target cells in the respiratory tract than does systemic administration. Gas phase contains several carcinogens such as benzene, formaldehyde, butadiene, N-nitrosodimethylamine and N-
nitrosodiethylamine and nitrogen oxides. Further nitrogen dioxide and nitrogen oxides of gas phase are capable of forming free radicals\textsuperscript{49}.

**COMPONENTS OF CIGARETTE SMOKE**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Whole smoke</th>
<th>Filtered smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrosamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNN\textsuperscript{a}</td>
<td>3.0±2.1</td>
<td>0.15±0.20</td>
</tr>
<tr>
<td>NNK\textsuperscript{a}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-nitrosodiethanolamine\textsuperscript{b}</td>
<td>3.9±3.5</td>
<td>0.29±0.28</td>
</tr>
<tr>
<td>N-nitrosodimethylamine\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>N-nitrosodiethylamine\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>N-nitrosopyrrolidine\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aromatic amines\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Aniline\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Bipyridyl\textsuperscript{b}</td>
<td>125±109</td>
<td>nd</td>
</tr>
<tr>
<td>2-Naphthylamine\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>4-Aminobiphenyl\textsuperscript{a}</td>
<td>14.2±1.2</td>
<td>nd</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\gamma)-butyrolactone\textsuperscript{b}</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>1,4-benzoquinone\textsuperscript{b}</td>
<td>263±177</td>
<td>nd</td>
</tr>
<tr>
<td>PAH\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naphthalene\textsuperscript{a}</td>
<td>422±60</td>
<td>239±8</td>
</tr>
<tr>
<td>Phenanthrene\textsuperscript{a}</td>
<td>8.6±2.8</td>
<td>0.65±0.13</td>
</tr>
<tr>
<td>Anthracene\textsuperscript{a}</td>
<td>2.2±1.6</td>
<td>0.06±0.01</td>
</tr>
<tr>
<td>Fluoranthrene\textsuperscript{a}</td>
<td>5.6±0.5</td>
<td>0.33±0.16</td>
</tr>
<tr>
<td>Pyrene\textsuperscript{a}</td>
<td>3.7±1.5</td>
<td>0.44±0.20</td>
</tr>
<tr>
<td>Chrysene\textsuperscript{a}</td>
<td>0.8±0.2</td>
<td>0.30±0.11</td>
</tr>
<tr>
<td>Benz[(\alpha)] Anthracene\textsuperscript{a}</td>
<td>4.1±2.9</td>
<td>0.12±0.02</td>
</tr>
<tr>
<td>Benzo[(\alpha)] Pyrene\textsuperscript{a}</td>
<td>1.7±0.8</td>
<td>0.04±0.01</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Compounds detected and confirmed by coelution with standards.

\textsuperscript{b}Compounds identified based upon mass spectrum library search results.

\textsuperscript{c}All are mean ± SD from 3 measurements

nd = not detectable (detection limit 10 ng/m\(^3\))
Bombick et al., have reported that the removal of carbonyls and other volatiles decreases the cytotoxicity of cigarette smoke (carcinogenic potential of the gas phase of environmental tobacco smoke).

Majority literature related to smoking is on the adverse effects of chronic smoking in humans. Cigarette smoke is a rich source of oxidant free radicals and a puff of cigarette smoke is known to contain more than $10^{18}$ spins/gram of tar, in tar phase. The inhaled cigarette smoke constituents (both gas and particulate constituents) interact with various plasma constituents, other cellular and membrane constituents especially lipids, proteins, nucleic acids resulting in the release of more number of free radicals in an amplified way causing a broad spectrum of effects, tissue damage and various diseases including cancers which can be grouped into cardiovascular, pulmonary, neurological disorders and miscellaneous type.

Harmful effects

Smoking has been implicated in the pathogenesis of various cardiovascular diseases including myocardial infarction, coronary heart disease, type II diabetes, hypertension and abnormal cardiopulmonary function. Free radicals inhaled with smoke and endogenously generated reactive oxygen derivatives enter into circulation and modulate antioxidant enzymes of blood and thereby cause cardiovascular problems. Though some controversy prevails over the effects of smoking on antioxidant enzyme activities it is clear that smoking is associated with disturbances by lowering antioxidant status. Gladstone et al., have reported that smoking impairs the antioxidant activity in the smokers serum. Strain et al have reported an elevation in the level of hemoglobin.
and ceruloplasmin but no significant effect on the antioxidant enzyme activities in the blood of smokers. Diken et al. have shown changes in the enzymatic and non-enzymatic antioxidant defense systems (decreased antioxidant status) of elderly smokers and attributed the same to oxidative stress caused by cigarette smoking. Surprisingly, Toth et al. hypothesized that the increased antioxidant activities and protective abilities of erythrocytes in cigarette smokers compared with erythrocytes of non-smokers. McGowan and Hanley have found high levels of iron and ferritin in alveolar macrophages of smokers and it is possible that changes in the iron metabolism with smoking may lead to increased availability of iron for oxidant reactions and result in impaired antioxidant activity of smokers' serum.

A study of Belgium population revealed that low levels of serum bilirubin in smokers may be associated with lower antioxidant activity. Durak et al. reported that cigarette smoke increased oxidants in erythrocytes and supplementation of antioxidants to smokers may be beneficial to decrease cellular oxidation damages. The only possible way to prevent and reduce adverse effects of smoking is through increasing antioxidant status. This is possible only through consumption of phytonutrients alone. While passing through different body parts and systems, certain toxic components of cigarette smoke may be neutralized by the antioxidants present respective tissues and in the blood. Therefore blood serves as a vehicle of cigarette smoke. Smoke is known to affect substantially several haemostatic factors leading to ischemic heart disease and the effects of smoking on haemostatic system remain for many years after giving up.

Balkayal et al., have shown that alcohol and smoking affected various blood variables in female and male mice and they found a more severe effect when combined
than alone\textsuperscript{64}. Zafer et al., have shown that smoking decreases erythrocyte count and hemoglobin level while increases leukocyte in general\textsuperscript{65}. Sharma et al., have reported that young asymptomatic male smokers tend to have hypertension, dislipidemia and increased production of free oxygen radicals perhaps by attenuation of oxidative stress by cigarette smoking and the subjects were set to be prone for premature coronary artery disease\textsuperscript{66}. Various studies repeatedly confirmed that cigarette smoking increases heart rate pulse and blood pressure, cardiac out put, stroke volume, velocity of contraction, myocardial contraction force and myocardial oxygen consumption, development of arrhythmia and alteration of electro cardiographic and ballisto cardiographic patterns\textsuperscript{66}.

Environmental tobacco smoke (ETS) represents a major risk factor for the generation of the diseases of the cardiovascular system. Endothelial cells of blood vessels are damaged as early as during the first month of life of passive smoking. Children with these defects can be detected during the 1\textsuperscript{st} decade of life. ETS over a period of more than ten years changes the intima/media ratio by enhancing the thickness of the vessel wall. Furthermore even at young age, cigarette smoking is associated with significant detrimental effects on cardiopulmonary function and exercise tolerance\textsuperscript{67}.

**Nitric Oxide vs. Cigarette smoking**

Nitric oxide has been shown to be involved in many regulatory functions of different tissues ranging from cardiovascular system to modulation of neuronal function. The multifaced biological effects of NO are furnished below.

Nitric oxide (NO) is a simple, free radical gas with important bio-regulatory functions in the nervous, immune and cardiovascular systems.
No synthase (NOS), EC.1.14.13.39 is an enzyme which generates NO from the terminal guanidine nitrogen of L-arginine during its conversion to citrulline. Three isoenzymes of NOS (nNOS, eNOS and iNOS) have been identified. They all require NADPH, tetrahydrobiopterene, flavin adenine dinucleotide and flavin mononucleotide as cofactors and all contain heme. Available data suggest that NO, the primary vasodilator produced by endothelial cells (ECs) is affected by cigarette smoking. Impaired endothelial dependent vasodilation (EDV) of different vessels leading to cardiovascular risk has been associated with cigarette smoking. Mainly a reduced endothelium dependent vasodilation seems to be one of the earliest path physiological effects of various...
risk factors for atherosclerosis preceding morphological changes in the vessel wall.

Moreover, atherosclerosis reduces transcription of mRNA for eNOS in endothelial cultures. Barua et al., have demonstrated an association between decreased NO production and reduced EDV. They found that reduced EDV, NO generation and eNOS activity in the presence of eNOS protein expression.69

Although direct infusion of nicotine may reduce nitric oxide mediated relaxation of mesenteric arteries, inhaled nicotine may maintain circulatory nitric oxide in humans.71,72 Nicotine could alter production of nitric oxide in several ways. (i) Through nicotine receptor activation of nitroxidergic nerves,73 endothelial cells or bypass receptor activation by directly interacting with biochemical pathways in endothelial cells. Alternately nicotine could alter activity of NOS, through production of oxygen derived free radicals. Since nicotine can cross cell membranes and affects the production of nitric oxide through interaction with the enzyme NOS. When administered separately, nicotine acts as a vasoconstrictor in vivo. However, when administered chronically vasodilation was observed. Potentially nicotine could exert opposite effect on same vessel.47 Effects of nicotine on nervous system are multifactorial, reflecting activity of nicotinic receptors of central and on peripheral autonomic ganglia.40 In typical doses achieved by smokers nicotine causes elevated alertness mild elevation in the blood pressure heart rate and gastrointestinal and urinary stimulations and for all these effects to which tolerance has been demonstrated. Barbera et al., have been demonstrated reduced expression of eNOS in pulmonary arteries and diminished synthesis of nitric oxide.75

Little information is available on acute effects of cigarette smoking on plasma NO and antioxidant levels. Certain studies indicated that cigarette smoke-
inhalation paradoxically increased NO concentration in plasma and enhanced vascular
dilation which is possibly due to exogenous NO contained in cigarette smoke. Tsuchiya
et al have observed that smoking a single cigarette temporarily decreased nitrate, nitrite
and serum antioxidant concentrations in plasma and they attributed these transient
changes to coronary vasoconstriction which is routinely observed after smoking\textsuperscript{57}.

Vleeming \textit{et al.}, opined that NO may contribute to the development of
cigarette smoking and nicotine addiction since (i) inhaled NO may facilitate increased
nicotine absorption (ii) NO released through nicotine reduces symptoms of stress, and (iii)
NO released endogenously by nicotine increases post synaptic dopamine levels. (iv)
NOS inhibitors attenuate symptoms of nicotinine abstinence syndrome\textsuperscript{76}.

COPD is a costly health problem and evidences suggest that oxidative stress of
smoking contributes to COPD. Antioxidant therapy seems to be beneficial in COPD\textsuperscript{11,51}.
Considerable evidence now links COPD with smoking induced oxidative stress. COPD is
an obstructive airway disorder characterized by a slowly progressive irreversible decrease
in FEV\textsubscript{1}; FEV\textsubscript{1} decreases are caused by a narrowing of airway lumen diameters that
develop as a result of varying perturbations in both airway and interstitial lung tissue.
Airway abnormalities consists of increased wall thickening intra luminal mucous
accumulation, smooth muscle hypertrophy and small air way lining fluid changes.
Additional early lesions include inflammatory cell infiltration and globet cell
metaplasia\textsuperscript{51}. 

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Figure: Cigarette smoke, oxidative stress and COPD. Numerous processes increase lung oxidative stress and contribute to a variety of abnormalities that contribute COPD.
Chronic bronchitis and chronic emphysema are two types of COPD and many risk factors such as cigarette smoke, air pollution, chemicals, heredity, and infectious and allergy conditions are implicated in the development of COPD. Cigarette smoking is known to decrease surfactant activity of bronchioalveolar lavage fluid. Chronic smoking resulted in irregular expansion of alveolar spaces and hypertrophy type II cells in rats. Studies revealed that cigarette smoking inhalation causes decreases in the level of lung surfactant phosphotidyl choline. While others reported there was no difference in lung lavage phospholipids concentration between smokers and non-smokers. Probably the heterogeneous nature of cigarette smoke might be responsible for observed discrepancy and this finding indicated that the effects of cigarette smoke on surfactant and surfactant producing cells are more complex. Since the secretion of surfactant is mediated by the action of catecholamines on specific beta adrenoreceptors in lungs and desensitization of adrenoreceptors in alveolar type II cells, it explains why smoke exposure will lower the surfactant level in bronchial preps. Reports reveal that direct and passive cigarette smoke exposure to guinea pigs causes a significant decrease in the level of a 36 Kda Ca^{2+} dependent phospholipids binding protein (PLBP) in alveolar type II cells and lung lavage.

Enough evidence suggests that smoking affects asthma adversely. Active smoking aggravates the problem and causes longitudinal changes in lung function and asthma-related mortality. Parental smoking, maternal smoking, and ETS exposure in patients with established asthma is associated with more severe symptoms and also with lower quality of life, reduced lung function, and increased health care utilization for asthma.
including hospital admission\textsuperscript{11,87}. ETS affects asthmatic children by impairing pulmonary function\textsuperscript{88}. When lung cancer cigarette components strongly damage proteins, lipids and DNA of the cells and defense machinery will be badly affected causing generation of toxic oxygen species and reactive metabolites generated by pulmonary metabolism of foreign compounds\textsuperscript{89}. Evidences clearly suggest that smoking is responsible for the causation of female lung cancer, and several other cancers, including squamous cell carcinoma, adrenocarcinoma\textsuperscript{11,90}. Tobacco related cancer become the most virulent and lethal cause of cancer mortality by the end of 20\textsuperscript{th} century\textsuperscript{91}. The rates of lung cancer in American men have greatly exceeded in Japanese men\textsuperscript{92}. Explanation for this was American manufactured cigarettes contain higher concentration of tobacco specifically nitrosamines, while much wider use of activated charcoal in the filters of Japanese than in American cigarettes\textsuperscript{92}.

Wang\textsuperscript{93} et al have reported that volatile compounds of cigarette smoke extracts acetaldehyde and acrolyne were able to inhibit human airway epithelial cell chemotoxis, proliferation and concentration of three dimensional collagen gels, a model of extra cellular matrix remodeling. Nonvolatile compounds of cigarette smoke extract also inhibited chemotoxis. Cigarette smoking contributes to architectural disruption present in the airway in COPD.

A number of studies suggested that cigarette smoking exerts an undefined biologic neuro protective influence against the development of the two neurodegenerative disorder Parkinson’s disease and Alzheimer’s disease\textsuperscript{28}. Various studies revealed that cigarette smoking may be neuro protective, activate NAChR (neuronal nicotine acetyl choline receptors) and inhibit monoaminoxidase in glial cells\textsuperscript{24}. Other studies also
support that up regulation of nicotinic receptors in the basal ganglia can provide partial protection against dopaminergic neurodegenerative processes. In humans cigarette smoking or administration of nicotine can activate NAcHRs leading to an increase of striatal dopaminergic activity effects that correlate with attenuation of tremor, rigidity and brachymenia and improved cognitive functions in PD patients.

Cigarette smoking vs. Ocular diseases

Now literature is accumulating to show smoking as an important and crucial cause for the development of certain major ocular diseases such as chronic irritable eye cataract, retinal vascular disorders, tobacco amblyopia, histic optic neuropathy thyroid eye disease, diabetic retinopathy, open angle glaucoma malignancy and age related macular degeneration. Besides many other ocular problems appear to be aggrivated in smokers. Smoking induces cataract formation by imposing an oxidative challenge thus contributing to the depletion of endogenous antioxidant pool. It is well known that oxidative damage plays a major role in cataract genesis. Further, tobacco smoke contains large amount of heavy metals like cadmium, lead, and copper which accumulate in lens and exert further toxicity. Smoking is also a risk factor for retinal artery occlusion. Smoking affects choroidal blood flow in the eye and promotes ischemia, hypoxia and micro infarctions and thereby increasing the susceptibility of the macula to degenerative changes. All these may lead to age related macular degeneration (ARMD).
References:

1. G.K. Gajalakshmi, Prabhat Jha, Kent Ranson, and Son Nguyen: Global patterns of smoking and smoking attributable mortality. *(Internet)*


